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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,584	08/30/2003	Vit Lauermann		8871

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EXAMINER	
CHANDRA, GYAN	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/651,584	LAUERMANN, VIT	
	Examiner	Art Unit	
	GYAN CHANDRA	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-17) in the reply filed on 2/13/2008 is acknowledged. Further, Applicant's election of species ((i) First moiety- an antibody, (ii) Second moiety- a sequence HSSKLQ, (iii) Type of inhibitor- IL-2 antibody, (iv) Active agent – IL-2, and (v) Reagent- PSA) with traverse in the reply filed on 4/11/2008 is acknowledged. However, applicant did not distinctly and specifically point out the supposed errors in the restriction requirement. Therefore, the Examiner does not provide any response to Applicant's traversal of species election.

The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, And/Or Claims

Claims 1-23 are pending.

Claims 18-23 are withdrawn from further consideration as being drawn to a nonelected Invention.

Claims 1-17 are under examination.

Specification

The abstract of the disclosure is objected to because the abstract should begin on a new page. Correction is required. See MPEP § 608.01(b).

That is, the claim(s), abstract and sequence listings (if any) should each begin on a new page since each of these sections (specification, abstract, claims, sequence

listings) of the disclosure are separately indexed in the Image File Wrapper (IFW). There should be no overlap on a single page of more than one section of the disclosure.

The abstract of the disclosure is objected to because the abstract comprises more than 150 words. See MPEP § 608.01(b).

The disclosure is objected to because it discloses either a nucleic acid sequence, amino acid sequence or both (e.g., pg. 30, 44) and these sequences are not in compliance as per 37 CFR 1.821-1.825. It is noted that a sequence identifier ("SEQ ID NO:X") must be used in order to be in sequence compliance as per 37 CFR 1.821-1.825.

Appropriate correction is required.

Claim Objections

Claims 2-5, 8 and 10-11 are objected to because of the following informalities:

Claims 2-3 are objected for reciting a number of non-elected first moieties (i.e., a soluble receptor, a cyclic peptide, a single chain antibody, a receptor, a chemokine, a nucleic acid, a peptide-lipid conjugate, a hormone or an antigen).

Claim 4 is objected for reciting a number of non-elected inhibitors (a peptide-nucleic acid inhibitor, a pepducin inhibitor, a nucleic acid/protein conjugate inhibitor, a receptor inhibitor, and others).

Claim 5 is objected for reciting a number of active agents (a chemical drug, a nucleic acid, a monoclonal antibody, a bispecific antibody, a single chain antibody, a cyclic peptide, a peptducin, a kinin system, a coagulation system and others).

Claims 8 and 10 are objected for reciting a number of second moieties (a lipid, a glycolipid, a nucleic acid, a phospholipid, a carbohydrate or many peptides having amino acid sequences e.g., SEQ IDs 2, 3, 4, 5,..... 108 and 109).

Claim 11 is objected for reciting a number of reagents (i.e., a lipase, nuclease, or a glycolytic enzyme).

The non-elected (non-allowed) species should be cancelled upon the allowance of any allowable subject matter.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 6, the phrase "second moiety is embedded within the first moiety" renders the claim indefinite because it is not clear if second moiety is a portion of second moiety or second moiety is a separate moiety and that it is structurally hidden in the first moiety or something else. Therefore, the meets and bound of the claim can not be determined.

Claim Rejections - 35 USC § 112, first paragraph-enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an inhibitor comprising (a) first moiety operably linked to (b) a second moiety, does not reasonably provide enablement for an inhibitor comprising (a) first moiety operably linked to (b) a second moiety wherein specific cleavage of second moiety causes reduction of binding, or activity of said inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to which the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breath of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

The instant disclosure fails to meet the enablement requirement for the following reasons:

Claims 1-17 are broadly drawn to an inhibitor which is deactivatable by a reagent produced by a target cell comprising: (a) first moiety operably linked to (b) a second

moiety wherein specific cleavage of second moiety causes reduction of binding, or activity of said inhibitor.

The state of the prior art and the predictability or lack thereof in the art:

Thorpe et al (US Patent No. 6,093,399) teach a composition comprising a bispecific antibody and a coagulant for tumor regression (see abstract). They teach a bispecific ligand comprising a "first binding region" that typically binds to a disease-related target cell, such as a tumor cell or to a component associated with such cell (column 3, lines 48+). They teach that the first binding region is operably linked to a "coagulant agent" which may be either a coagulation factor itself or may be a second binding region that is capable of binding to a coagulation factor (col. 3, lines 55+). They teach that the first binding regions and any second binding regions, may be antibodies or fragment thereof (col. 4, lines 5+). D'Amico et al (US Patent No. 6,368,598) teach making a drug complex comprising peptide attached with a drug through another small peptide (linker) which is cleavable by prostate specific antigen (PSA) and the complex is an inhibitor as it inhibits growth of prostate cancer cells (Fig. 3-4 and col. 2, lines 30+). Mhaka et al (Bioorg. Med. Chem. Letters 12: 2459-2461, 2002) teach making an inhibitor for prostate cancer by attaching 5-fluorodeoxyuridine prodrug to a peptide sequence which is specifically cleaved by PSA produced by prostate cancer cells and as a result cancer cell proliferation is inhibited (page 2459, right column). Gillies et al (US Patent No. 7,091,321) teach making a fusion of IL-2 and Fc receptor (Fig.4). Gillies et at teach that proteins can be joined together through either chemical or genetic

manipulation using methods known in the art (col. 1, lines 38+). They teach making fusion proteins between an immunoglobulin moiety and second non-immunoglobulin moieties (col. 2, lines 43+). Gillies et al teach that a non-immunoglobulin moiety can be a cytokine such as IL-2, Il-4, IL-4, IL-5.....IL-16 or IL-18 (col. 3, lines 48+). The art does not teach that the cleavage of said fusion protein by removing second moiety would always result in reduced activity of said fusion protein. This can only happen when a fusion protein is always more inhibitory than any moiety (the first moiety or second moiety) when used alone. Therefore, it is unpredictable and would require a large amount of experimentation to determine if all the inhibitors comprising (a) first moiety operably linked to (b) a second moiety when specifically cleaved the second moiety would always result in reduction of binding, or activity of said inhibitor.

The amount of direction and guidance present and the presence or absence of working examples: Given the teachings found in the art, detailed teachings are required to be present in the disclosure in order to enable the skilled artisan to practice the invention as claimed. These teachings are absent. The specification on pg.41-44 teaches making a dimer of extracellular domain (ECD) of human TNFR-2 with MMP cleavage (Example 1). The specification on pg. 44- 47 teaches making a fusion of anti-IL-2 antibody, anti-EGFR antibody or anti-HER2 antibody with a peptide comprising PSA cleavage site (Examples 2-4). The specification does not disclose any example of an inhibitor comprising (a) first moiety operably linked to (b) a second moiety, wherein when said second moiety is specifically cleaved said inhibitor would more likely than not

result in reduction of binding, or activity. Therefore, it is unpredictable how one of the skill in the art can practice the instantly claimed invention.

The breadth of the claims and the quantity of experimentation needed: Due to the large amount of experimentation necessary to make and use an inhibitor comprising (a) first moiety operably linked to (b) a second moiety when specifically cleaved the second moiety would always result in reduced binding, or activity of said inhibitor, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the state of the prior art which establishes the unpredictability about making and using the same, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

For the purpose of comparing the claims with the prior art, it is noted that "an inhibitor which is deactivatable by a reagent produced by a target cell comprising: (a) first moiety operably linked to (b) a second moiety wherein specific cleavage of second moiety causes reduction of binding, or activity of said inhibitor." is being interpreted as "an inhibitor that can be deactivated by any reagent produced by a target cell, wherein said inhibitor would be less active upon cleavage of the moiety only when moieties (a) and (b) are more active

together than any of the two moieties alone." It is noted that (a) first moiety and (b) second moiety are not produced in nature as a hybrid molecule.

Claims 1-5, 7-9, 11, 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Thorpe et al (US Patent No. 6,093,399).

The instant claims are broadly drawn to an inhibitor which is deactivatable by a reagent produced by a target cell comprising: (a) first moiety operably linked to (b) a second moiety wherein specific cleavage of said second moiety causes reduction of binding, or activity of said inhibitor, wherein said first moiety is a polypeptide, a peptide, an antibody, a bispecific antibody (claims 2-3); wherein said inhibitor is a bispecific antibody inhibitor (claims 4); wherein said active agent is a bispecific antibody or a coagulation factor (claim 5); wherein said first and second moieties are connected by a peptide, or a chemical linker (claim 7); wherein second moiety is selected from the group consisting of a peptide, a lipid, a polypeptide, a carbohydrate, a polysaccharide, a glycolipid, a nucleic acid or a conjugate thereof (claim 8); wherein said second moiety is a peptide which comprises a sequence cleavable by protease (claim 9); wherein said inhibitor of claim 1 is selected from the group consisting of a protease, a lipase, a nuclease, or glycolytic enzyme (claim 11); wherein said reagent is produced by endothelial cells, activated or proliferating endothelial cells or tumor cells (claim 13); wherein the inhibitor alone or inhibitor with an active agent is in a biodegradable polymer, in a slow release implant, in a microcapsulated composition, or conjugate with a biodegradable polymer (claim 14); wherein the inhibitor of claim 1 further comprises or associates with a recognition domain that binds to a target cell surface marker, an

extracellular matrix or component thereof (claim 15); wherein said recognition domain binds to tumor cells (claim 16); and wherein said recognition domain is selected from the group consisting of an antibody, a monoclonal antibody, a bispecific antibody..... a tissue factor or compositions and variants thereof (claim 17).

Thorpe et al teach making binding ligands for inhibiting tumor comprising a "first binding region" that typically binds to a disease related target cell, such as tumor cell or a component associated with such a cell and the first binding region is operably linked to another agent such as a "coagulating agent" (column 3, lines 47+). They teach that "bispecific" molecule comprise at a minimum, two functionally distinct regions. They teach that the first binding regions and any second binding regions, may be antibodies or fragment thereof (col. 4, lines 5+). Thorpe et al teach that the majority of such tumor-binding ligands are contemplated to be agents, particularly antibodies, that bind to a cell surface tumor antigen or marker (col. 5, lines 16+). They teach that such bispecific agents may be fusion proteins prepared by molecular biological techniques (col. 9, lines 50+). Thorpe et al teach that bispecific agents can be linked by various methods known in the art including use of peptide spacers, such as L-Leu-L-Ala-Leu-L-Ala (col. 52, lines18+). Thorpe et al teach preparing various formulations of said binding ligands. Thorpe et al teach that a fusion protein is cleaved by endogenous proteases present in target tissues (tumor cells) for example, metalloproteinases, thrombin, factor Xa, plasmin (col.88, lines 28+). Thorpe et al do not specifically say that which moiety a protease would cleave, but cleaving the fusion protein and relieving one moiety from other would anticipated the instant invention. They teach that the inhibitor (bispecific

agents) can be enclosed in hard or soft shell gelatin capsule (which is a natural polymer), or compressed into tablets (col. 67, 55+). Therefore, the prior art of record explicitly or implicitly anticipates the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thorpe et al as applied to claims 1-5, 7-9, 11, 13-17 above, and further in view of Mhaka et al (Bioorg. Med. Chem. Letters 12: 2459-2461, 2002); or Thorpe et al as applied to claims 1-5, 7-9, 11, 13-17 above, and further in view of D'Amco et al (US Patent No. 6,368,598 published on 4/9/2002).

The instant claims are further drawn to an inhibitor which is deactivatable by a reagent produced by a target cell comprising: (a) first moiety operably linked to (b) a

second moiety wherein specific cleavage of said second moiety causes reduction of binding, or activity of said inhibitor, wherein second moiety is SEQ ID NO: 17 (HSSKLQ) (claim 10); and wherein said reagent is a prostate specific antigen (claim 12).

The teachings of Thorpe et al are summarized as set forth supra. Thorpe et al do not teach a bispecific molecule wherein a second moiety is a peptide having amino acid sequence of SEQ ID NO: 17 (which is HSSKLQ) and wherein a reagent that cleaves the peptide of SEQ ID NO: 17 is a prostate specific antigen.

Mhaka et al do teach a peptide of SEQ ID NO: 17 (HSSKLQ) which is used for targeted delivery of cytotoxic agents to sites of metastatic prostate cancer (see abstract and page 2460, left column). They teach that the peptide HSSKLQ is PSA specific peptide substrate that is efficiently cleaved by the enzyme activity of this protease. Therefore, they teach a reagent (protease) which is a prostate specific antigen and it cleaves the peptide HSSKLQ.

D'Amico et al teach a drug complex for delivery of a drug or other agent to a target cell comprising a targeting carrier molecule which is selectively distributed to specific cell type, a linker which is acted upon by a molecule present in the specific cell and a drug or agent to be delivered to the specific cell type (see abstract, Fig on page 6). They teach that the polypeptide which is used for delivering an agent can be of sequence HSSKLQ (SEQ ID NO: 17) and figure on the bottom of Col. 6. They teach that PSA is a protease which recognizes the peptide bond between a polypeptide of SEQ ID NO: 13 and another molecule as shown in the figure on the bottom of column 6.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to use a peptide such as HSSKLQ for targeted delivery in tumors such as prostate metastasis where a reagent such as PSA cleaves the peptide HSSKLQ as taught by Mhaka et al or D'Amico et al. The person of ordinary skill in the art would have been motivated do so to make an inhibitor for tissue specific targeted delivery of an antibody, protein, or drugs as taught by Mhaka et al or D'Amico et al. One would have a reasonable expectation of success in making an inhibitor with a second moiety of the peptide HSSKLQ which can be cleaved by PSA to release the inhibitor in a targeted tissue as taught by D'Amico et al or Mhaka et al.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GYAN CHANDRA whose telephone number is (571)272-2922. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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